

RAPID, HIGH-YIELDING AND RECYCLABLE CeO₂-CATALYZED PROTOCOL FOR THE SYNTHESIS OF 4-PHENYL-1,3-THIAZOLE-2-AMINES: A GREEN ALTERNATIVE TO CONVENTIONAL METHODS

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ABSTRACT

The present study describes a CeO₂-catalyzed heterogeneous protocol for the synthesis of substituted 4-phenyl-1,3-thiazol-2-amine derivatives under recyclable and environmentally preferable reaction conditions. It uses the heterogeneous catalyst cerium oxide under mild conditions. The cyclo-condensation of different substituted phenacyl bromides and thiourea was carried out in ethanol at 80°C in the presence of 10 mol% CeO₂. The bifunctional acid-base nature of the oxide surface coupled with the dual redox character of cerium which switches between its +3 and +4 state jointly with the bifunctional acid-base nature of the oxide surface promote the simultaneous activation of the electrophilic and nucleophilic partners and hence the efficient construction of the C-S and C-N bonds required to close the ring. The streamlined process provided the respective thiazole-2-amine products in isolated yields between 86 and 91 within a mere 3 hours. Ten structurally different congeners, substituted with electron-rich and electron-deficient substituents distributed across ortho-, meta-, and para-positions of the phenyl ring, were successfully accessed, which highlights the broad functional-group compatibility of the approach. The catalyst was easily separated by simple filtration and could be reused in four consecutive runs with insignificant attenuation of activity. The use of ethanol as a non-toxic solvent also contributes to the environmental merits of the protocol. This plan provides a cost-saving, green and easily implementable platform to assemble biologically relevant thiazole frameworks and precludes the further functional and pharmacological studies of the resulting frameworks. Furthermore, the developed methodology aligns with United Nations Sustainable Development Goal (SDG) 12: Responsible Consumption and Production through the use of a recyclable heterogeneous catalyst, environmentally benign ethanol as solvent, reduced reaction time, and minimized waste generation.

Keywords: Cerium Oxide, Green Chemistry, Thiazole Synthesis, Heterogeneous Catalysis, One-Pot Synthesis, Phenacyl Bromide, Thiazole-2-Amine.

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INTRODUCTION

The thiazoles, five-membered aromatic rings containing one sulfur atom and one nitrogen atom, are of particular interest within this category.¹⁻³ They are found in abundance in naturally occurring metabolites, clinically relevant pharmaceuticals and crop-protection agents, where they confer antimicrobial, antineoplastic, anti-inflammatory, antitubercular and other therapeutic effects.⁴⁻⁶ The 4-phenyl-1,3-thiazole-2-amine motif and its close structural analogues represent especially attractive platforms, as they readily lend themselves to further derivatization and they often have desirable pharmacological profiles. Several studies have determined that thiazol-2-amine analogues with various substituents have significant antileishmanial, antimicrobial, and enzyme-modulating properties, which drives onward attempts to design new analogues with better performance.⁷⁻⁹ Traditional methods of thiazole-bearing amines generally involve long, multi-step sequences, severe reaction conditions, and/or risky reagents, none of which are sustainable and/or efficient. A comparative list of these catalytic systems to date, including zinc chloride (ZnCl₂), iron(III) chloride(FeCl₃), copper(I) iodide(CuI), palladium-supported catalysts, elemental iodine, ionic liquids, and magnetically retrievable nanocatalysts, each has specific shortcomings, such as requiring high temperatures, lengthy reaction times, stoichiometric quantities of activator, cumbersome catalyst separation, prohibitive costs, or residual metal traces in the products.¹⁸⁻²⁰ A comparative table of these catalytic systems to date, including zinc chloride (ZnCl₂), iron(III) chloride(FeCl₃), copper(I) iodide(CuI), palladium-supported catalysts, elemental iodine, ionic liquids, and magnetically retrievable nano catalysts, each have specific shortcomings, such as require high temperatures,

lengthy reaction times, stoichiometric quantities of activator, cumbersome catalyst separation, prohibitive costs, or residual. The increasing tide of support of green chemistry principles has thus led to a surge of interest in heterogeneous catalysts that are not only environmentally friendly but also easy to handle, recycle, and have the capability to increase not only selectivity but also yield.^{10–13} Cerium dioxide (CeO₂), also known as ceria, is an oxide of a transition metal, with unusual redox characteristics due to the readily reversible couple of Ce 4+/Ce 3+ plus the abundance of oxygen-vacancy defects on its surface. Its outer layer also contains Lewis-acidic cerium centers and basic oxide anions present in tandem. Despite the existing body of work investigating the use of CeO₂ nanostructures in the investigation of organic transformations, including multicomponent assemblies, oxidations, and condensations, the application of CeO₂ nanostructures in the preparation of thiazole has remained relatively understudied.^{14–17,26} It is against this background that we reveal herein a CeO₂-promoted preparation of 4-phenyl-1, 3-thiazole-2-amine derivatives without any precedence in the literature. The described strategy explicitly lays stress on the environmentally responsible and economically viable conditions, with the two-fold objective of achieving high yields within a shortened reaction window and uncomplicated recovery of catalysts. Our work aims to augment the repertoire of sustainable methodologies to access pharmacologically interesting derivatives of heterocyclic compounds and to provide a stepping stone to downstream functional and biological evaluation of the resulting derivatives. In addition, the present work supports Sustainable Development Goal (SDG) 12: *Responsible Consumption and Production* by promoting greener synthetic practices through catalyst recyclability, safer solvents, and improved resource efficiency.

EXPERIMENTAL

Material and Methods

All reagents and chemicals used in this study were obtained from commercial vendors (Sigma-Aldrich, Merck, and Spectrochem) and were used as received without further purification, except where otherwise indicated. Cerium oxide (CeO₂) nanoparticles, with an average particle size below 25 nm and a stated purity of $\geq 99.5\%$, were obtained. Both the substituted phenacyl bromides and thiourea were of analytical-reagent grade. Ethanol of analytical-reagent grade ($\geq 99.9\%$) served as the reaction medium throughout. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60 F₂₅₄ aluminum-backed sheets (Merck) developed in a hexane/ethyl acetate mixture (8:3, v/v), with visualization under ultraviolet illumination at 254 nm. Melting points were measured by the open-capillary technique using a digital melting-point apparatus and were not corrected.

Characterization Method

The Spectroscopic and analytical characterization of the prepared compounds was performed using the techniques outlined below. Fourier-transform infrared (FT-IR) spectra were acquired on a Bruker ALPHA FT-IR spectrophotometer using KBr pellets over the 4000–400 cm⁻¹ window. Proton nuclear magnetic resonance (¹H NMR) spectra were obtained on a Bruker FT-NMR 500 MHz spectrometer in DMSO-d₆, with tetramethylsilane (TMS) as the internal reference; chemical shifts are reported in parts per million (δ ppm). Carbon-13 NMR (¹³C NMR) spectra were measured on the same instrument operating at 100 MHz]. Mass spectrometric analyses were conducted on a quadrupole mass spectrometer equipped with an electrospray ionization (ESI) interface. Quantitative determination of carbon, hydrogen, nitrogen, and sulfur content was performed on a Elementar Vario EL III CHNS analyzer.

General Procedure for the Synthesis of 4-Phenyl-1,3-Thiazole-2-Amine Derivatives

In a typical experiment, the appropriate substituted phenacyl bromide (1 mmol), thiourea (1.2 mmol), and CeO₂ (10 mol%) were combined with ethanol (5 mL) in a 25 mL round-bottom flask fitted with a magnetic stir bar and a reflux condenser. The resulting suspension was stirred at 80°C for 3 hours, with reaction progress monitored periodically by TLC. Upon completion, the mixture was allowed to cool to ambient temperature and then subjected to vacuum filtration to recover the heterogeneous CeO₂ catalyst. The collected filtrate was poured over crushed ice (25 g), whereupon the solid product precipitated. The crude solid was isolated by filtration, rinsed with cold water (2 $\times$ 10 mL), and finally purified by recrystallisation from hot ethanol to afford the corresponding 4-phenyl-1,3-thiazole-2-amine derivative in analytically pure form.

Catalyst Recyclability Procedure

After each catalytic run, the recovered CeO₂ was rinsed in succession with ethanol (2 × 5 mL) and distilled water (2 × 5 mL), then dried at 110 °C for 2 hours in an oven before redeployment in the next reaction cycle under identical conditions. This recycling sequence was repeated for four consecutive cycles.

Analytical Data of Synthesized Compounds**4-(4-chlorophenyl)-1, 3-thiazol-2-amine (1c)**

Melting point: 266 °C; Yield: 89%; ¹H NMR (500 MHz, DMSO-d₆) δ: 7.61–7.37 (m, Ar-H), 3.37 (s), 2.15–2.05 (m).

¹³C NMR (125 MHz, DMSO-d₆) δ (ppm): 168.9, 148.4, 139.9, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 104.3, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm⁻¹): 3345, 3052, 2361, 2174, 1967, 1941, 1685, 1585, 1453, 1420, 1307, 1210, 1125, 1088, 1048, 1031, 953, 826, 763, 731, 688, 612, 586.

MS (m/z): 210.96 (base peak), 212.91, 214.14, 182.17, 109.91, 107.93, 273.09, 577.55

4-(4-methoxyphenyl)-1, 3-thiazol-2-amine (1d)

Melting point: 252 °C; Yield: 90%; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61–7.37 (m), 3.37 (s), 2.15–2.05 (m); residual solvent peaks at δ 2.50 (DMSO-d₆) and 3.33 (H₂O).

¹³C NMR (125 MHz, DMSO-d₆) δ (ppm): 168.7, 149.3, 148.9, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 104.3, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm⁻¹): 3052, 2925, 2852, 2152, 1899, 1601, 1576, 1536, 1515, 1452, 1416, 1362, 1328, 1245, 1195, 1103, 1039, 1025, 952, 826, 751, 718, 674, 620, 588.

MS (m/z): 207.02 (base peak), 208.16, 209.06, 242.27, 269.12, 340.13, 411.13, 441.14, 107.94, 102.02

4-(4-Fluorophenyl)-1, 3-thiazol-2-amine (1e)

Melting point: 219 °C; Yield: 88%; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61–7.37 (m), 3.37 (s), 2.15–2.05 (m); residual solvent peaks observed at δ 2.50 (DMSO-d₆) and 3.33 (H₂O).

¹³C NMR (125 MHz, DMSO-d₆) δ (ppm): 168.9, 160.6, 159.3, 149.0, 148.6, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 121.7, 118.8, 104.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm⁻¹): 3047, 1933, 1660, 1597, 1537, 1518, 1486, 1451, 1421, 1343, 1256, 1229, 1142, 1108, 1031, 1009, 958, 907, 874, 834, 809, 780, 747, 671, 643, 606, 585.

MS (m/z): 194.97 (base peak), 196.11, 197.01, 210.97, 236.08, 258.09, 259.17

4-(4-nitrophenyl)-1, 3-thiazol-2-amine (1f)

Melting point: 230 °C; Yield: 89%; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61–7.37 (m), 3.37 (s), 2.15–2.05 (m); residual solvent peaks at δ 2.50 (DMSO-d₆) and 3.33 (H₂O).

¹³C NMR (125 MHz, DMSO-d₆) δ (ppm): 168.8, 159.9, 149.0, 148.7, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 104.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm⁻¹): 3053, 2217, 1958, 1687, 1597, 1509, 1459, 1428, 1339, 1179, 1129, 1075, 1046, 954, 849, 758, 635, 610, 584.

MS (m/z): 221.98 (base peak), 242.27, 243.35, 150.07, 107.94, 102.03, 360.36, 387.26, 403.19, 479.36, 495.38

4-(2-Nitrophenyl)-1, 3-thiazol-2-amine (1g)

Melting point: 220 °C; Yield: 87%; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61–7.37 (m), 3.37 (s), 2.15–2.05 (m); residual solvent signals at δ 2.50 (DMSO-d₆) and 3.33 (H₂O).

¹³C NMR (125 MHz, DMSO-d₆) δ (ppm): 168.8, 148.9, 148.5, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 104.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm⁻¹): 3552, 3403, 3122, 2327, 2176, 2026, 1861, 1619, 1523, 1387, 1285, 1105, 1029, 899, 723, 631, 587

MS (m/z): 221.96 (base peak), 236.08, 258.10, 259.20, 243.98, 245.14, 224.02, 223.14, 211.03, 274.08

4-(3-nitrophenyl)-1, 3-thiazol-2-amine (1h)

Melting point: 270 °C; Yield: 86%; ¹H NMR (500 MHz, DMSO-d₆) δ 7.61–7.37 (m), 3.37 (s), 2.15–2.05 (m); residual solvent signals at δ 2.50 (DMSO-d₆) and 3.33 (H₂O).

^{13}C NMR (125 MHz, DMSO- d_6) δ (ppm): 168.8, 148.9, 147.8, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 124.3, 121.7, 104.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm^{-1}): 3056, 1610, 1475–1332, 1214–1000, 876–689

MS (m/z): 439.14 (base peak), 437.14, 220.05, 190.04, 112.90, 248.97, 325.25, 399.13, 469.23, 471.23, 535.14, 722.34, 800.21, 979.91; 221.99 (base peak), 223.13, 182.15, 101.99, 353.31, 495.10, 577.54, 605.60, 633.64, 661.69, 717.75, 955.98

4-(4-iodophenyl)-1, 3-thiazol-2-amine (1i)

Melting point: 250°C; Yield: 88%; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.74–7.53 (m, Ar-H), 3.31 (s, H_2O), 2.50 (s, DMSO).

^{13}C NMR (125 MHz, DMSO- d_6) δ (ppm): 168.9, 148.9, 148.6, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 124.3, 121.7, 104.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm^{-1}): 3552–3288, 3121, 1619, 1522–1387, 1328–1029, 899–587

MS (m/z): 302.97 (base peak), 304.07, 305.00, 241.07, 182.14, 109.93, 107.92, 346.12, 441.37, 577.55, 605.61, 633.64, 661.68, 717.77, 955.99

4-(3-Chlorophenyl)-1, 3-thiazol-2-amine (1j)

Melting point: 210°C; Yield: 90%; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.39–6.92 (m, Ar-H), 3.31 (s, H_2O), 2.50 (s, DMSO).

^{13}C NMR (125 MHz, DMSO- d_6) δ (ppm): 168.9, 149.0, 148.7, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 124.3, 121.7, 103.0, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm^{-1}): 3311–3126, 2920, 1599, 1515–1427, 1321–1027, 953–578

MS (m/z): 210.95 (base peak), 212.84, 214.12, 101.99, 301.18, 413.30, 605.57, 685.50, 873.67

4-(3-bromophenyl)-1, 3-thiazol-2-amine (1k)

Melting point: 285°C; Yield: 89%; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.96–6.93 (m, Ar-H), 3.31 (s, H_2O), 2.50 (s, DMSO).

^{13}C NMR (125 MHz, DMSO- d_6) δ (ppm): 168.9, 149.0, 148.8, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 124.3, 121.7, 103.2, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

FTIR (cm^{-1}): 3310–3122, 2918–2849, 1589, 1515–1408, 1335–998, 954–575

MS (m/z): 256.98 (base peak), 254.94, 258.07, 259.01, 182.18, 109.89, 107.93, 102.03, 319.16, 441.48, 507.33, 605.57, 633.63, 661.69, 717.78, 718.84, 853.55, 956.05

4-(3-methylphenyl)-1, 3-thiazol-2-amine (1l)

Melting point: 205°C; Yield: 91%; ^1H NMR (500 MHz, DMSO- d_6) δ : 7.82–7.03 (m, Ar-H), 3.31 (s, H_2O), 2.50 (s, DMSO).

^{13}C NMR (125 MHz, DMSO- d_6) δ (ppm): 168.9, 149.0, 148.7, 139.7, 135.8, 133.9, 131.6, 129.6, 128.8, 126.9, 124.3, 121.7, 104.4, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1.

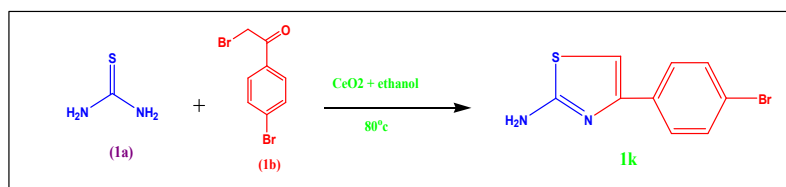
FTIR (cm^{-1}): 3450–3295, 3113–2915, 1632, 1534–1486, 1328–1033, 846–563

MS (m/z): 191.04, 437.26, 438.28, 439.30, 305.15, 306.24, 192.17, 193.04, 102.00, 601.46

RESULTS AND DISCUSSION

Optimization of Catalyst Loading

The reaction parameters governing the CeO_2 -mediated assembly of 4-phenyl-1,3-thiazole-2-amine were fine-tuned stepwise, using phenacyl bromide (1 mmol) and thiourea (1.2 mmol) as the model substrates, dissolved in ethanol (5 mL) and stirred at 80 °C. Reaction progress was monitored by thin-layer chromatography with a hexane/ethyl acetate (8:3) eluent (Scheme-1). After completion, the heterogeneous CeO_2 catalyst was collected by filtration; the filtrate was poured over crushed ice, and the precipitated crude product was purified by recrystallisation from hot ethanol.



Scheme-1: Thiourea (1a) + Phenacyl bromide (1b) $\rightarrow$ 4-(4-Bromophenyl)-1,3-thiazol-2-amine (1k); CeO_2 (10 mol%), EtOH, 80°C, 3 h

To determine the optimal catalyst loading, the CeO₂ content was systematically varied from 0 to 15 mol%, while all other variables were held constant (Table-1). At room temperature without a catalyst, only trace product was detected even after 5 hours, confirming the indispensable role of CeO₂ in driving the cyclisation step. At 3 mol%, the isolated yield was only 42% after 4 hours, indicating incomplete substrate conversion. Incremental increases to 5 mol% and then to 10 mol% produced pronounced gains, with the latter delivering the desired thiazole in 90% isolated yield over 3 hours. Further increasing the loading to 15 mol% produced no measurable improvement, suggesting that the available substrate had become saturated on the catalyst surface. On this basis, a CeO₂ loading of 10 mol% was selected as optimal and adopted for all subsequent transformations.

Table-1: Effect of Catalyst Loading on the Synthesis of the Model Compound (1k)

Entry	Catalyst Loading (mol %)	Temp. (°C)	Time (h)	Isolated Yield (%)
1	None (control)	RT	5	Traces
2	CeO ₂ (3)	80	4	42
3	CeO ₂ (5)	80	3	75
4*	CeO ₂ (10)	80	3	90
5	CeO ₂ (15)	80	3	90

* Optimal entry. Reaction conditions: Phenacyl bromide (1 mmol), thiourea (1.2 mmol), CeO₂ (variable mol %), ethanol (5 mL). Isolated yield after recrystallisation from hot ethanol.

Solvent Optimization Study

A methodical solvent-screening exercise was conducted to identify the most appropriate reaction medium (Table-2). Four discrete combinations were assessed at a constant CeO₂ loading of 10 mol% at 80°C: pure ethanol, an ethanol/water mixture (1:1, v/v), and pure methanol, alongside a corresponding catalyst-free benchmark. The use of pure ethanol at 80°C in conjunction with 10 mol% CeO₂ (Entry 2) afforded the best outcome, yielding the product in 90% yield over only 3 hours. Switching to a 1:1 ethanol/water binary medium (Entry 3) caused a dramatic drop in yield to 15% even after 5 hours; this decline can be rationalized by the competitive adsorption of water molecules onto the Lewis-acidic surface sites of CeO₂, thereby diminishing the catalyst's ability to activate the electrophilic phenacyl bromide. Methanol (Entry 4) furnished only a 10% yield after 6 hours, an outcome plausibly linked to its lower boiling point, which restricts the accessible reaction temperature, as well as differences in substrate solvation behaviour. Ethanol was retained as the standard solvent in all subsequent investigations.

Table-2: Effect of Solvent on the CeO₂-Catalyzed Synthesis of 4-Phenyl-1,3-Thiazole-2-Amine

Entry	Solvent	Catalyst (mol %)	Temp. (°C)	Time (h)	Yield (%)
1	Ethanol	None	RT	6	Traces
2*	Ethanol	CeO ₂ (10)	80	3	90
3	EtOH:H ₂ O (1:1)	CeO ₂ (10)	80	5	15
4	Methanol	CeO ₂ (10)	80	6	10

*Optimal entry. Reaction conditions: Phenacyl bromide (1 mmol), thiourea (1.2 mmol), CeO₂ (10 mol %), solvent (5 mL). Isolated yield after recrystallisation

Comparison with Previously Reported Catalytic Systems

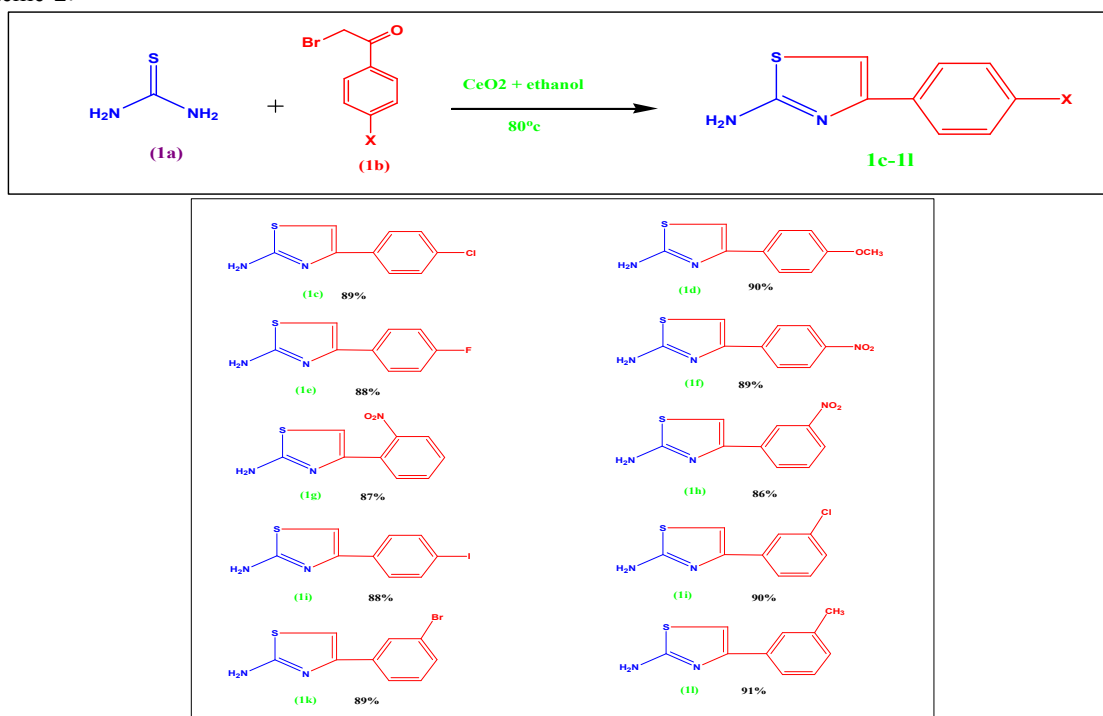
To place the present work in context, Table-3 presents a comprehensive comparison of catalytic systems previously employed for the synthesis of thiazole and thiazol-2-amine derivatives. Classical Lewis acid catalysts such as ZnCl₂¹⁸ and FeCl₃¹⁹ require elevated temperatures (100–120°C), prolonged reaction times (8–12 hours), and toxic solvents (DMSO, DMF), with the added disadvantage of difficult catalyst recovery. Transition-metal catalysts such as CuI²⁰ and Pd/C²⁸ offer improved selectivity but incur high cost and pose a risk of product contamination by trace metals. Halogen-mediated (I₂)²² and ionic liquid-based²¹ methods present issues of stoichiometric reagent consumption and difficult product separation, respectively. Magnetic nanocatalysts^{23,24,26} offer the advantage of magnetic recovery but often require lengthy reaction times (4–16 hours) or complex multi-step catalyst preparation. The CeO₂-catalyzed protocol described herein addresses these limitations by combining a mild temperature (80°C), a short reaction time (3 hours), a green solvent (ethanol), straightforward catalyst recovery by filtration and excellent product yields (86–91%).

Table-3: Comparison of Catalytic Systems for the Synthesis of Thiazole / Thiazol-2-Amine Derivatives

Catalyst	Solvent	Temp. (°C)	Time (h)	Ref.
ZnCl ₂	DMSO	120	10–12	18
FeCl ₃	DMF	100	8	19
CuI	Toluene	110	10	20
Pd/C	EtOH	90	6	28
I ₂ (stoichiometric)	MeCN	80	5	22
[Bmim]-type IL	Ionic liquid	85	6	21
Ca/4-MePy-IL@ZY-Fe ₃ O ₄	EtOH	80	16	23
FeNPs/C	H ₂ O	RT	5–8	24
Electrochemical I ⁻	Electrochem. cell	RT	4–8	25
SPIONs	EtOH	RT	4–6	26
Ni@Zeolite-Im-IL	EtOH/DMSO	80	3–5	27
CeO ₂ (This work)	EtOH	80	3	—

Substrate Scope and Generality

With the optimal reaction parameters established (10 mol% CeO₂, ethanol, 80 °C), the scope of the protocol was evaluated by synthesizing a panel of 10 4-phenyl-1,3-thiazole-2-amine analogs from a structurally diverse set of phenacyl bromides (Table-4). Substituents spanning electron-withdrawing groups (EWGs: nitro, halogen, iodo) and electron-donating groups (EDGs: methyl, methoxy) were examined at the ortho-, meta-, and para-positions of the phenacyl bromide's aromatic ring as seen in Scheme-2.



Scheme-2: General Reaction for Substrate Scope – Thiourea (1a) + Substituted Phenacyl Bromides (1b) Products (1c–1l); CeO₂ (10 mol%), EtOH, 80 °C

Phenacyl bromides bearing electron-withdrawing para-substituents consistently delivered the corresponding products in high isolated yields (86–90%) within 3 hours. The increased electrophilicity of the carbonyl carbon imparted by these EWGs facilitates nucleophilic attack by the thiourea sulfur, thereby accelerating the rate-limiting cyclisation. Substrates carrying electron-donating groups, namely methyl and methoxy, likewise furnished outstanding yields (90–91%); however, those bearing nitro substituents at ortho- or meta-positions required marginally longer durations (3.5 hours), consistent with the steric perturbations these groups introduce to the cyclisation geometry. Taken together, all the substrates examined produced the desired thiazole-2-amine derivatives in good to excellent isolated yields (86–91%), thereby substantiating the broad functional-group compatibility of the CeO₂-driven methodology. From a sustainability perspective, the present

protocol offers several advantages, including the use of ethanol as a green solvent, catalyst recovery by simple filtration, and catalyst reuse over multiple cycles. These features reduce chemical waste and improve process efficiency, thereby supporting the principles of green chemistry and *SDG 12*.

Table-4: Substrate Scope for the Synthesis of 4-Phenyl-1,3-Thiazole-2-Amine Derivatives

Compound	Substituent (X)	Isolated Yield (%)	Time (h)
1c	4-Cl	89	3
1d	4-OCH ₃	90	3
1e	4-F	88	3
1f	4-NO ₂	89	3
1g	2-NO ₂	87	3.5
1h	3-NO ₂	86	3.5
1i	4-I	88	3
1j	2-Cl	90	3
1k	4-Br	89	3
1l	4-CH ₃	91	3

Reaction conditions: Substituted phenacyl bromide (1 mmol), thiourea (1.2 mmol), CeO₂ (10 mol %), ethanol (5 mL), 80°C. Isolated yield after recrystallisation.

CONCLUSION

In conclusion, a sustainable, operationally simple, and ecologically benign CeO₂-catalyzed protocol has been successfully developed for the one-pot construction of previously unreported 4-phenyl-1,3-thiazole-2-amine derivatives. Operating under the optimized reaction parameters (10 mol% CeO₂, ethanol, 80°C, 3 hours), the procedure delivered 10 structurally varied analogues in good to excellent isolated yields, ranging from 86 to 91%. The methodology proved compatible with a wide spectrum of functional groups, encompassing both electron-donating and electron-withdrawing substituents as well as sterically encumbered ortho-substituted derivatives. Owing to its heterogeneous nature, the CeO₂ catalyst could be conveniently retrieved by filtration and reapplied across four successive cycles with only marginal attenuation of activity. The combined attributes of using ethanol as a green solvent, the abbreviated reaction time, the high product yields, and the demonstrated catalyst recyclability collectively position this protocol as a viable and sustainable alternative to existing literature methods. Subsequent investigations will focus on in-depth biological screening of the newly synthesized thiazole-2-amine derivatives against antimicrobial, anticancer, and enzyme-inhibitory targets. The methodology also contributes to *SDG 12 (Responsible Consumption and Production)* by providing an environmentally responsible and resource-efficient route for the synthesis of biologically important thiazole derivatives.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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